Local kinetics of morphogen gradients: SI Text

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1 Mathematical preliminaries

Here we present the precise mathematical statements of the basic results related to the considered class of partial differential equations that are used throughout our paper. Consider a general initial boundary value problem

$$\begin{cases} u_t = u_{xx} + f(t,x,u) & (t,x) \in (0,\infty) \times (0,\infty), \\ u_x(t,0) = -g(t) & t \in (0,\infty), \\ u(0,x) = u_0(x) & x \in [0,\infty). \end{cases} \tag{1.1}$$

where by solution $u = u(t,x) \in \mathbb{R}$ we mean the classical solution of the problem in (1.1), i.e., a function $u \in \mathcal{A}$, where $\mathcal{A} := C^{1,2}((0,\infty) \times [0,\infty)) \cap C([0,\infty) \times [0,\infty)) \cap L^\infty((0,\infty) \times (0,\infty))$ (for notation and further details, see e.g. [1]). Well-posedness of problem (1.1) in the considered class is well-known under some mild regularity assumptions on f, g and u_0, including all situations considered in the present paper (see e.g. [2, 1, 3])

Our main tool for constructing the upper and lower bounds for the local accumulation time is the parabolic comparison principle, which, in its general form in the case of one-dimensional quasilinear parabolic equations can be stated as:

Proposition 1.1 (Parabolic comparison principle) *Let f satisfy*

$$|f(t,x,u_1) - f(t,x,u_2)| \leq L|u_1 - u_2|, \tag{1.2}$$

for some $L > 0$, all $(t,x) \in [0,\infty) \times [0,\infty)$, and all u_1, u_2 satisfying $|u_1|, |u_2| \leq M$, for some $M > 0$. Then, every solution $\overline{u}, \underline{u} \in \mathcal{A}$ of differential inequalities

$$\begin{cases} \overline{u}_t \geq \overline{u}_{xx} + f(t,x,\overline{u}) & (t,x) \in (0,\infty) \times (0,\infty), \\ \overline{u}_x(t,0) \leq -g(t) & t \in (0,\infty), \\ \overline{u}(0,x) \geq u_0(x) & x \in [0,\infty), \end{cases} \tag{1.3}$$

and

$$\begin{cases} \underline{u}_t \leq \underline{u}_{xx} + f(t,x,\underline{u}) & (t,x) \in (0,\infty) \times (0,\infty), \\ \underline{u}_x(t,0) \geq -g(t) & t \in (0,\infty), \\ \underline{u}(0,x) \leq u_0(x) & x \in [0,\infty), \end{cases} \tag{1.4}$$

such that $|\overline{u}|, |\underline{u}| \leq M$ satisfies

$$\underline{u}(t,x) \leq \overline{u}(t,x) \quad \textit{for all} \quad (t,x) \in [0,\infty) \times [0,\infty). \tag{1.5}$$

Proof. The proof follows from [4, Theorem 10 and Remark (ii) of Chap. 3, Sec. 6] applied to $w = \underline{u} - \overline{u}$ and using (1.2) (see also [2, 5]). ■

The functions $\underline{u}$ and $\overline{u}$ above are called sub- and supersolutions for the problem in (1.1). Moreover, since the solution $u(t,x)$ of (1.1) is both super- and subsolution, it holds

$$\underline{u}(t,x) \leq u(t,x) \leq \overline{u}(t,x) \quad \text{for all} \quad (t,x) \in [0,\infty) \times [0,\infty). \tag{1.6}$$

That is, the solution of problem (1.1) is squeezed between its sub- and supersolutions.

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2 Approach to the steady state

Now consider the steady version of (1.1) with

$$f(t,x,u) = -k(u)u, \qquad g(t) = \alpha. \tag{2.1}$$

where $\alpha > 0$ is a given constant and $k > 0$ is a given continuously differentiable function, corresponding to secretion at the boundary and bulk degradation with a local concentration feedback control. The steady state $v > 0$ for (1.1) and (2.1) satisfies

$$v_{xx} - k(v)v = 0, \qquad v_x(0) = -\alpha, \qquad v(\infty) = 0. \tag{2.2}$$

A straightforward integration of this equation yields

$$v_x = -G(v), \qquad G(v) = \sqrt{2\int_0^v sk(s)ds}, \tag{2.3}$$

where we noted that by elliptic regularity the limit as $x \to \infty$ in (2.2) also holds for v_x (see e.g. [1]). In particular, in view of the strict monotonic increase of $G(v)$ on $[0,\infty)$, for every $\alpha > 0$ there exists a unique constant $v_0 = v_0(\alpha) > 0$ solving $G(v_0) = \alpha$, provided that $G(\infty) = \infty$ (true in all cases considered in this paper). Furthermore, in this case the solution of (2.2) is given parametrically by

$$\int_{v(x)}^{v_0} \frac{ds}{G(s)} = x. \tag{2.4}$$

Note that this formula defines the solution for all $x > 0$, since the integral in (2.4) diverges as $v \to 0^+$. Thus, for every $\alpha > 0$ there exists a unique positive classical solution of (2.2) and (2.1), which is strictly monotonically decreasing and goes to zero together with its derivative as $x \to \infty$.

Now, choosing $\underline{u}(t,x) = 0$ and $\overline{u}(t,x) = v(x)$ as sub- and supersolution, respectively, one can see that the solution of the initial value problem in (1.1) with $g(t) = \alpha$ exists globally in time (see e.g. [2, 3]) and remains bounded between 0 and v for all times:

$$0 \le u(t,x) \le v(x) \le M < \infty, \tag{2.5}$$

where $M = v(0) = v_0(\alpha)$. In particular, the solution $u(t,x)$ of (1.1) and (2.1) is uniformly bounded, is monotonically increasing in time for every $x \ge 0$ (see the argument at the end of Methods in the main text) and converges to the stationary solution by, e.g., the arguments of [6, Theorem 3.6]. Hence by Dini's theorem the solution approaches v from below uniformly on every compact subset of $[0,\infty)$. Finally, since $\lim_{x\to\infty} v(x) = 0$, in view of (2.5) this convergence is in fact uniform on the whole of $[0,\infty)$.

3 Equivalent definitions of the accumulation time

For bounded monotonically increasing solutions of the initial boundary value problem in (1.1) the accumulation time $\tau(x)$ is defined as the expectation value (possibly infinite a priori) of $t \in (0,\infty)$ with respect to the probability measure $p(t,x)dt$ [7]:

$$\tau(x) = \int_0^\infty tp(t,x)dt, \qquad p(t,x) = \frac{1}{v(x)}\frac{\partial u}{\partial t}(t,x). \tag{3.1}$$

Since $p(\cdot,x) \in C((0,\infty))$ for every $x \ge 0$, it is convenient to rewrite this formula in terms of u, using integration by parts:

$$\tau(x) = \frac{1}{v(x)}\int_0^\infty (v(x) - u(t,x))dt. \tag{3.2}$$

However, this step requires a justification, since for nonlinear problems we do not in general have an a priori decay estimate ensuring that the boundary term arising during integration by parts does not contribute. To circumvent this difficulty, let us introduce a cutoff function $\eta \in C^\infty(\mathbb{R})$, such that $\eta(t) = 1$ for all $t < 1$ and $\eta(t) = 0$ for all $t > 2$. Then, using monotone convergence theorem, we have

$$\begin{aligned}
\int_0^\infty tp(t,x)dt &= \lim_{\varepsilon\to 0^+}\left(\frac{1}{v(x)}\int_0^\infty tu_t(t,x)\eta(\varepsilon t)dt\right)\\
&= \lim_{\varepsilon\to 0^+}\left(\frac{1}{v(x)}\int_0^\infty (v(x)-u(t,x))\eta(\varepsilon t)dt + \frac{1}{v(x)}\int_0^\infty (v(x)-u(t,x))\,\varepsilon t\,\eta'(\varepsilon t)dt\right)\\
&= \frac{1}{v(x)}\int_0^\infty (v(x)-u(t,x))dt + \lim_{\varepsilon\to 0} R_\varepsilon(x), \qquad (3.3)\\
|R_\varepsilon(x)| &\leq \left(\frac{2\max|\eta'(t)|}{v(x)}\int_{\varepsilon^{-1}}^\infty (v(x)-u(t,x))dt\right) \to 0 \qquad \text{as } \varepsilon\to 0 \quad \forall x\in[0,\infty),
\end{aligned}$$

yielding (3.2) under the assumption that the right-hand side of (3.2) is bounded. Our upper bound constructions will show that the latter is true for all situations considered.

4 Equation $u_t = u_{xx} - u^n$

In what follows we construct an estimate to

$$\hat{\tau}_n(x) = \frac{1}{v(x)}\int_0^\infty (v(x)-u(t,x))\,dt, \tag{4.1}$$

where $u \in \mathcal{A}$ is the solution for the following problem:

$$\begin{cases} u_t = u_{xx} - u^n & (t,x)\in(0,\infty)\times[0,\infty),\\ u_x(t,0) = -\alpha & t\in(0,\infty),\\ u(0,x) = 0 & x\in[0,\infty), \end{cases} \tag{4.2}$$

and v solves

$$\begin{cases} v_{xx} - v^n = 0 & x\in[0,\infty),\\ v_x(0) = -\alpha, & v(\infty) = 0, \end{cases} \tag{4.3}$$

respectively, where $n \in \mathbb{N}$ and $\alpha > 0$ are some given constants. The case of $n = 1$ admits a closed form solution and was treated previously in [7]. The solution of (4.3) for any $n > 1$ is explicitly

$$v(x) = \left(2\frac{(n+1)}{(n-1)^2}\right)^{\frac{1}{n-1}} (x+a)^{-\frac{2}{n-1}}, \tag{4.4}$$

where

$$a = \frac{2^{\frac{n}{n+1}}(n+1)^{\frac{1}{n+1}}\alpha^{\frac{1-n}{1+n}}}{n-1}. \tag{4.5}$$

Here and everywhere below the algebraic computations are performed, using Mathematica 7.0 software.

4.1 Case $n = 2$

As the first step we explicitly consider the important particular case $n = 2$. We define the difference

$$w(t,x) = v(x) - u(t,x). \tag{4.6}$$

Subtracting (4.3) from (4.2) and setting $n = 2$, we have

$$\begin{cases} w_t = w_{xx} - (u+v)w & (t,x)\in(0,\infty)\times[0,\infty),\\ w_x(t,0) = 0 & t\in(0,\infty),\\ w(0,x) = v & x\in[0,\infty). \end{cases} \tag{4.7}$$

Also, by (2.5), we have

$$0 \leq w(t,x) \leq v(x) \quad (t,x)\in(0,\infty)\times[0,\infty). \tag{4.8}$$

A direct inspection shows that the functions $\overline{w}$ and $\underline{w}$ satisfying

$$\begin{cases} \overline{w}_t = \overline{w}_{xx} - v\overline{w} & (t,x) \in (0,\infty) \times [0,\infty) \\ \overline{w}_x(t,0) = 0 & t \in (0,\infty), \\ \overline{w}(0,x) = v & x \in [0,\infty), \end{cases} \tag{4.9}$$

and

$$\begin{cases} \underline{w}_t = \underline{w}_{xx} - 2v\underline{w} & (t,x) \in (0,\infty) \times (0,\infty), \\ \underline{w}_x(t,0) = 0 & t \in (0,\infty), \\ \underline{w}(0,x) = v & x \in [0,\infty), \end{cases} \tag{4.10}$$

are super- and subsolutions for the problem (4.7), respectively, that is

$$\overline{w}_t - \overline{w}_{xx} + (u+v)\overline{w} = u\overline{w} \geq 0, \tag{4.11}$$

$$\underline{w}_t - \underline{w}_{xx} + (u+v)\underline{w} = -(v-u)\underline{w} \leq 0, \tag{4.12}$$

$$w_x = \overline{w}_x = \underline{w}_x = 0. \tag{4.13}$$

Here we took into account (2.5) and positivity of $\overline{w}$ and $\underline{w}$, which, again, follows from the comparison principle for (4.9) and (4.10), using zero as subsolution. Therefore, by comparison principle we have

$$\underline{w}(t,x) \leq w(t,x) \leq \overline{w}(t,x) \tag{4.14}$$

Next we consider the Laplace transforms of $\overline{w}$ and $\underline{w}$:

$$\overline{w}(x,s) = \int_0^\infty \overline{w}(t,x)e^{-st}dt, \quad \underline{W}(x,s) = \int_0^\infty \underline{w}(t,x)e^{-st}dt, \qquad s > 0. \tag{4.15}$$

Thanks to (2.5), the following estimates hold

$$\overline{W}(x,s) \leq \frac{M}{s}, \quad \underline{W}(x,s) \leq \frac{M}{s} \tag{4.16}$$

so that $\overline{W}(x,s)$ and $\underline{W}(x,s)$ are well defined for each $s > 0$ and $x \in [0,\infty)$.

On the other hand in a view of monotone convergence theorem we have

$$\lim_{s\to 0^+} \overline{W}(x,s) = \int_0^\infty \overline{w}(t,x)dt, \qquad \lim_{s\to 0^+} \underline{W}(x,s) = \int_0^\infty \underline{w}(t,x)dt, \tag{4.17}$$

where the limits above could possibly evaluate to $+\infty$. Now, since

$$\hat{\tau}_2(x) = \frac{1}{v(x)} \int_0^\infty w(t,x)dt \tag{4.18}$$

we deduce from (4.17) that

$$\frac{1}{v(x)} \lim_{s\to 0^+} \underline{W}(x,s) \leq \hat{\tau}_2(x) \leq \frac{1}{v(x)} \lim_{s\to 0^+} \overline{W}(x,s) \tag{4.19}$$

Let us evaluate $\overline{W}(x,s)$ and $\underline{W}(x,s)$. Applying Laplace transform to equations (4.9) and (4.10) we have:

$$\begin{cases} \overline{W}_{xx} - (v+s)\overline{W} = -v, & (x,s) \in (0,\infty) \times [0,\infty) \\ \overline{W}_x(0,s) = 0 & s \in (0,\infty) \\ \overline{W}(x,s) < \frac{M}{s} & (x,s) \in [0,\infty) \times (0,\infty) \end{cases} \tag{4.20}$$

and

$$\begin{cases} \underline{W}_{xx} - (2v+s)\underline{W} = -v, & (x,s) \in [0,\infty) \times (0,\infty) \\ \underline{W}_x(0,s) = 0 & s \in (0,\infty) \\ \underline{W}(x,s) < \frac{M}{s} & (x,s) \in [0,\infty) \times (0,\infty) \end{cases} \tag{4.21}$$

The condition involving the limit at infinity is a direct consequence of the estimate (4.16) and allows to rule out exponentially growing modes for solutions of (4.20) and (4.21).

The solution of problem (4.3) (the function $v(x)$) which is needed for solving (4.20) and (4.21) takes a particularly simple form (see (4.4)):

$$v(x) = \frac{6}{(x+a)^2}, \qquad a = \left(\frac{12}{\alpha}\right)^{1/3}. \tag{4.22}$$

Similarly, problems (4.20) and (4.21) admit exact analytical solutions. Let us start with the solution of the boundary value problem problem (4.20). As can be verified by direct substitution, the two functions:

$$\overline{W}_1(x,s) = \frac{e^{-\sqrt{s}(a+x)}\left(s(a+x)^2 + 3\sqrt{s}(a+x) + 3\right)}{\sqrt{\pi}s^{5/4}(a+x)^2}, \tag{4.23}$$

$$\overline{W}_2(x,s) = \frac{e^{\sqrt{s}(a+x)}\left(s(a+x)^2 - 3\sqrt{s}(a+x) + 3\right)}{\sqrt{\pi}s^{5/4}(a+x)^2} \tag{4.24}$$

are two linearly independent solutions of the homogeneous equation

$$\overline{W}_{xx} - (v+s)\overline{W} = 0, \quad (x,s) \in [0,\infty) \times (0,\infty) \tag{4.25}$$

Next, having (4.23) and (4.24), we apply the variation of parameters formula to obtain a particular solution of the equation

$$\overline{W}_{xx} - (v+s)\overline{W} = -v, \quad (x,s) \in [0,\infty) \times (0,\infty) \tag{4.26}$$

$$\tag{4.27}$$

which turns out to be simply

$$\overline{W}_p(x,s) = \frac{6}{s(x+a)^2} \tag{4.28}$$

To solve the boundary value problem (4.20), we write the general solution

$$\overline{W}_g(x,s) = C_1\overline{W}_1(x,s) + C_2\overline{W}_2(x,s) + \overline{W}_p(x,s) \tag{4.29}$$

and choose constants C_1, C_2 in such a way that both the side conditions in (4.20) are satisfied. It is easy to observe that the boundedness condition at $x \to \infty$ requires $C_2 = 0$, and the second condition at $x = 0$ fixes the constant C_2. After simple algebraic manipulations we have that

$$\overline{W}(x,s) = \frac{6}{s(x+a)^2}\left(1 - \frac{2e^{-\sqrt{s}x}\left(s(a+x)^2 + 3\sqrt{s}(a+x) + 3\right)}{a\sqrt{s}\left(a^2 s + 3a\sqrt{s} + 6\right) + 6}\right) \tag{4.30}$$

solves the boundary value problem (4.20). Evaluating the limit of the above expression we obtain

$$\lim_{s\to 0^+} \overline{W}(x,s) = 1. \tag{4.31}$$

This result is more transparently seen from a series expansion of $\overline{W}(x,s)$ around $s = 0$. Since $\overline{W}(x,s)$ in (4.30) is a meromorphic function of $\sqrt{s}$ for each x, it can be expanded into the Laurent series around $s = 0$ by Taylor expansion of the exponential functions involved in (4.30). The result of the computation shows that the contributions of all the poles in the series vanish and the leading order terms in the expansion are:

$$\overline{W}(x,s) = 1 - \frac{s\left(a^4 + (a+x)^4\right)}{4(a+x)^2} + O(s^{3/2}), \tag{4.32}$$

implying (4.31).

A similar computation allows to obtain the solution for problem (4.21). Let us follow the basic steps in construction of this solution. The two linearly independent solution corresponding to the homogeneous problem is

$$\underline{W}_1(x,s) = \frac{e^{-\sqrt{s}(a+x)}\left(\sqrt{s}(a+x)\left(s(a+x)^2 + 6\sqrt{s}(a+x) + 15\right) + 15\right)}{\sqrt{\pi}s^{7/4}(a+x)^3}, \tag{4.33}$$

$$\underline{W}_2(x,s) = \frac{e^{\sqrt{s}(a+x)}\left(\sqrt{s}(a+x)\left(s(a+x)^2 - 6\sqrt{s}(a+x) + 15\right) - 15\right)}{\sqrt{\pi}s^{7/4}(a+x)^3} \tag{4.34}$$

Applying variation of parameters, we also obtain a particular solution of the corresponding inhomogeneous equation

$$\begin{aligned}\underline{W}_p(x,s) = {} & \frac{3}{4s^{3/2}(a+x)^3} \times \Big(15\sqrt{s}(a+x) + \\ & \operatorname{Chi}\left(\sqrt{s}(a+x)\right)\left(3\left(2s(a+x)^2+5\right)\sinh\left(\sqrt{s}(a+x)\right) - \sqrt{s}(a+x)\left(s(a+x)^2+15\right)\cosh\left(\sqrt{s}(a+x)\right)\right) + \\ & \operatorname{Shi}\left(\sqrt{s}(a+x)\right)\left(\sqrt{s}(a+x)\left(s(a+x)^2+15\right)\sinh\left(\sqrt{s}(a+x)\right) - 3\left(2s(a+x)^2+5\right)\cosh\left(\sqrt{s}(a+x)\right)\right)\Big),\end{aligned} \tag{4.35}$$

where Shi(x) and Chi(x) stand for the integral sine and cosine functions, respectively [8].

Next, forming the general solution out of (4.33), (4.34) and (4.35) and choosing the constants to satisfy the side conditions at $x = 0$ and $x \to \infty$ we obtain the solution of the boundary value problem (4.21)

$$\underline{W}(x,s) = \underline{W}_p(x,s) + C(s)\underline{W}_1(x,s) \tag{4.36}$$

where

$$\begin{aligned}C(s) = {} & -\frac{3\sqrt{\pi}}{4}\frac{s^{1/4}e^{a\sqrt{s}}}{a^4s^2+6a^3s^{3/2}+21a^2s+45a\sqrt{s}+45} \times \Big(a\sqrt{s}\left(a^2s+45\right) + \\ & \operatorname{Chi}\left(a\sqrt{s}\right)\left(\left(a^2s\left(a^2s+21\right)+45\right)\sinh\left(a\sqrt{s}\right) - 3a\sqrt{s}\left(2a^2s+15\right)\cosh\left(a\sqrt{s}\right)\right) + \\ & \operatorname{Shi}\left(a\sqrt{s}\right)\left(3a\sqrt{s}\left(2a^2s+15\right)\sinh\left(a\sqrt{s}\right) - \left(a^2s\left(a^2s+21\right)+45\right)\cosh\left(a\sqrt{s}\right)\right)\Big)\end{aligned} \tag{4.37}$$

The function above has the following expansion around $s = 0$:

$$\underline{W}(x,s) = \frac{1}{2} - \frac{\left(2a^5+3x^5\right)s}{60x^3} + O\left(s^2\log s\right), \tag{4.38}$$

from which it follows immediately that

$$\lim_{s\to 0^+}\underline{W}(x,s) = \frac{1}{2}. \tag{4.39}$$

Combining (4.31), (4.39) with (4.19) and (4.22) we have:

$$\frac{(x+a)^2}{12} \le \hat{\tau}_2(x) \le \frac{(x+a)^2}{6} \tag{4.40}$$

4.2 Case of arbitrary integer $n \geq 2$

In the case of arbitrary $n \in \mathbb{N}$, $n \geq 2$, the strategy for obtaining the estimates for $\hat{\tau}_n$ is identical to the one used in the previous section for the $n = 2$ case. First let w be as in (4.6). Next, subtracting equations (4.3) and (4.2), we have

$$\begin{cases} w_t = w_{xx} - \left(\displaystyle\sum_{k=1}^{n} u^{k-1}v^{n-k}\right) w & (x,t) \in [0,\infty)\times(0,\infty), \\ w_x(t,0) = 0 & t \in (0,\infty), \\ w(0,x) = v & x \in [0,\infty). \end{cases} \tag{4.41}$$

By comparison principle, using zero as a subsolution, we have $w \geq 0$ and thus (2.5) holds. This observation and (4.41) immediately gives that the function $\underline{w} \geq 0$ satisfying

$$\begin{cases} \underline{w}_t = \underline{w}_{xx} - nv^{n-1}\underline{w} & (t,x) \in (0,\infty)\times[0,\infty), \\ \underline{w}_x(t,0) = 0 & t \in (0,\infty), \\ \underline{w}(0,x) = v & x \in [0,\infty), \end{cases} \tag{4.42}$$

is a subsolution, and the function $\overline{w} \geq 0$ satisfying

$$\begin{cases} \overline{w}_t = \overline{w}_{xx} - v^{n-1}\overline{w} & (t,x) \in (0,\infty)\times[0,\infty), \\ \overline{w}_x(t,0) = 0 & t \in (0,\infty), \\ \overline{w}(0,x) = v & x \in [0,\infty), \end{cases} \tag{4.43}$$

is a supersolution for problem (4.41). The function $v(x)$ for each n is given by (4.4).

We apply arguments identical to these of previous section concerning Laplace transform of functions $\overline{w}(t,x)$ and $\underline{w}(t,x)$ to end up with the following equations for $\overline{W}(x,s)$ and $\underline{W}(x,s)$ (defined as before by (4.15))

$$\begin{cases} \overline{W}_{xx} - (v^{n-1}+s)\overline{W} = -v & (x,s) \in [0,\infty)\times(0,\infty), \\ \overline{W}_x(s,0) = 0 & s \in (0,\infty), \\ \overline{W}(x,s) \le \frac{M}{s} & (x,s) \in [0,\infty)\times(0,\infty), \end{cases} \tag{4.44}$$

and

$$\begin{cases} \underline{W}_{xx} - (nv^{n-1}+s)\underline{W} = -v & (x,s) \in [0,\infty)\times(0,\infty), \\ \underline{W}_x(s,0) = 0 & s \in (0,\infty), \\ \underline{W}(x,s) \le \frac{M}{s} & (x,s) \in [0,\infty)\times(0,\infty). \end{cases} \tag{4.45}$$

The accumulation time can be then estimated in terms of solutions of the problems (4.44) and (4.45) as follows

$$\frac{1}{v(x)} \lim_{s\to 0^+} \underline{W}(x,s) \le \hat{\tau}_n(x) \le \frac{1}{v(x)} \lim_{s\to 0^+} \overline{W}(x,s). \tag{4.46}$$

4.3 Case $n = 3$

The explicit solutions for problems (4.44) and (4.45) for increasing values of n become exceedingly cumbersome. Therefore, in the remainder of this section we limit ourselves to the case $n = 3$. In this case

$$v(x) = \frac{\sqrt{2}}{x+a}, \qquad a = \left(\frac{2}{\alpha^2}\right)^{1/4}. \tag{4.47}$$

The solutions of problems (4.44) and (4.45) are obtained by exactly the same steps as those used for solving problems (4.20) and (4.21). They lead to

$$\overline{W}(x,s) = \frac{\sqrt{2}}{s(x+a)}\left(1 - \frac{e^{-\sqrt{s}x}\left(\sqrt{s}(a+x)+1\right)}{a^2 s + a\sqrt{s}+1}\right) \tag{4.48}$$

and

$$\begin{aligned} \underline{W}(x,s) = {} & A(s)\frac{e^{-\sqrt{s}(a+x)}\left(s(a+x)^2+3\sqrt{s}(a+x)+3\right)}{\sqrt{\pi}s^{5/4}(a+x)^2} + \frac{1}{\sqrt{2}s^{3/2}(a+x)^2} \times \Big(3\sqrt{s}(a+x) + \\ & \sinh\left(\sqrt{s}(a+x)\right)\left(\left(s(a+x)^2+3\right)\operatorname{Chi}\left(\sqrt{s}(a+x)\right) + 3\sqrt{s}(a+x)\operatorname{Shi}\left(\sqrt{s}(a+x)\right)\right) \\ & - \cosh\left(\sqrt{s}(a+x)\right)\left(3\sqrt{s}(a+x)\operatorname{Chi}\left(\sqrt{s}(a+x)\right) + \left(s(a+x)^2+3\right)\operatorname{Shi}\left(\sqrt{s}(a+x)\right)\right)\Big), \end{aligned} \tag{4.49}$$

where

$$\begin{aligned} A(s) = {} & \frac{\pi}{2}\frac{e^{a\sqrt{s}}}{\sqrt[4]{s}\left(a\sqrt{s}\left(a^2 s + 3a\sqrt{s}+6\right)+6\right)} \times \\ & \Big(\operatorname{Chi}\left(a\sqrt{s}\right)\left(a\sqrt{s}\left(a^2s+6\right)\cosh\left(a\sqrt{s}\right) - 3\left(a^2s+2\right)\sinh\left(a\sqrt{s}\right)\right) + \\ & \operatorname{Shi}\left(a\sqrt{s}\right)\left(3\left(a^2s+2\right)\cosh\left(a\sqrt{s}\right) - a\sqrt{s}\left(a^2s+6\right)\sinh\left(a\sqrt{s}\right)\right) - 6a\sqrt{s}\Big). \end{aligned} \tag{4.50}$$

These two functions have the following expansions around $s = 0$:

$$\overline{W}(x,s) = \frac{a^2+(a+x)^2}{\sqrt{2}(a+x)} - \frac{\sqrt{2}\sqrt{s}\left(2a^3+(a+x)^3\right)}{3(a+x)} + O(s), \tag{4.51}$$

and

$$\begin{aligned} \underline{W}(x,s) = {} & \frac{a^3+2(a+x)^3}{6\sqrt{2}(a+x)^2} + \frac{s}{900\sqrt{2}(a+x)^2}\Big(15\left(3a^5+2(a+x)^5\right)\log(s) + 18(5\gamma-6)a^5 \\ & +90a^5\log(a) - 25a^3(a+x)^2 + 4(15\gamma-23)(a+x)^5 + 60(a+x)^5\log(a+x)\Big) + O\left(s^{3/2}\right), \end{aligned} \tag{4.52}$$

respectively. In the equation above $\gamma \approx 0.577216$ is the Euler's constant. As a consequence, we have

$$\lim_{s\to 0^+} \overline{W}(x,s) = \frac{a^2+(x+a)^2}{\sqrt{2}(x+a)}, \quad \lim_{s\to 0^+} \underline{W}(x,s) = \frac{a^3+2(x+a)^3}{6\sqrt{2}(x+a)^2}, \tag{4.53}$$

and so

$$\frac{a^3+2(x+a)^3}{12(x+a)} \le \hat{\tau}_3(x) \le \frac{a^2+(x+a)^2}{2}. \tag{4.54}$$

4.4 Case $n = 4$

In the case $n = 4$ the stationary solution for (4.2) reads

$$v(x) = \left(\frac{10}{9}\right)^{1/3} \frac{1}{(x+a)^{2/3}}, \qquad a = \left(\frac{80}{243\alpha^3}\right)^{1/5}. \tag{4.55}$$

Once again, the solutions of problems (4.44) and (4.45) are obtained by exactly the same steps as those used for solving problems (4.20) and (4.21). They lead to the following formulas:

$$\overline{W}(x,s) = A(s)(x+a)^{1/2} K_{\frac{7}{6}}\left(\sqrt{s}(x+a)\right) - \left(\frac{10}{9}\right)^{1/3} \frac{\left({}_0F_1\left(;-\frac{1}{6};\frac{1}{4}s(x+a)^2\right)-1\right)}{s(x+a)^{2/3}}, \tag{4.56}$$

where

$$A(s) = \frac{2\left(9\sqrt[3]{30}a^2 s\,{}_0F_1\left(;\frac{5}{6};\frac{a^2 s}{4}\right) + 2\sqrt[3]{30}\,{}_0F_1\left(;-\frac{1}{6};\frac{a^2 s}{4}\right) - 2\sqrt[3]{30}\right)}{9a^{7/6}s\left(a\sqrt{s}K_{\frac{1}{6}}\left(a\sqrt{s}\right) - K_{\frac{7}{6}}\left(a\sqrt{s}\right) + a\sqrt{s}K_{\frac{13}{6}}\left(a\sqrt{s}\right)\right)}, \tag{4.57}$$

and

$$\begin{aligned}
&\underline{W}(x,s) = B(s)\sqrt{a+x}K_{\frac{13}{6}}\left(\sqrt{s}(a+x)\right) + \frac{1}{26}\left(\frac{5}{36}\right)^{1/3}(a+x)^{4/3} \times \\
&\left(9\,{}_0F_1\left(;\frac{19}{6};\frac{1}{4}s(a+x)^2\right)\,{}_1F_2\left(-\frac{2}{3};-\frac{7}{6},\frac{1}{3};\frac{1}{4}s(a+x)^2\right)\right. \\
&\left.+4\,{}_0F_1\left(;-\frac{7}{6};\frac{1}{4}s(a+x)^2\right)\,{}_1F_2\left(\frac{3}{2};\frac{5}{2},\frac{19}{6};\frac{1}{4}s(a+x)^2\right)\right),
\end{aligned} \tag{4.58}$$

where

$$\begin{aligned}
B(s) = &\frac{1}{10374}\left(\frac{5}{36}\right)^{1/3}\left[a^{13/6}s^{13/12}\left(5320\,{}_0F_1\left(;-\frac{7}{6};\frac{a^2 s}{4}\right)\,{}_1F_2\left(\frac{3}{2};\frac{5}{2},\frac{19}{6};\frac{a^2 s}{4}\right)\right.\right. \\
&\left.-19152\,{}_0F_1\left(;\frac{19}{6};\frac{a^2 s}{4}\right)\,{}_1F_2\left(-\frac{2}{3};-\frac{7}{6},\frac{1}{3};\frac{a^2 s}{4}\right)\right) + a^{25/6}s^{25/12} \times \\
&\left(1368\,{}_0F_1\left(;-\frac{1}{6};\frac{a^2 s}{4}\right)\,{}_1F_2\left(\frac{3}{2};\frac{5}{2},\frac{19}{6};\frac{a^2 s}{4}\right) - 1134\,{}_0F_1\left(;\frac{25}{6};\frac{a^2 s}{4}\right)\,{}_1F_2\left(-\frac{2}{3};-\frac{7}{6},\frac{1}{3};\frac{a^2 s}{4}\right)\right) \quad (4.59) \\
&1197\; 2^{5/6}a^{13/6}s^{7/6}\Gamma\left(-\frac{7}{6}\right)\,{}_0F_1\left(;\frac{19}{6};\frac{a^2 s}{4}\right) I_{-\frac{13}{6}}\left(a\sqrt{s}\right) \\
&\left.-38304\; 2^{1/6}\Gamma\left(\frac{19}{6}\right)\,{}_0F_1\left(;-\frac{7}{6};\frac{a^2 s}{4}\right) I_{\frac{13}{6}}\left(a\sqrt{s}\right)\right]\Big/\left[a^{4/3}s^{13/12} \times\right. \\
&\left.\left(a\sqrt{s}K_{\frac{7}{6}}\left(a\sqrt{s}\right) - K_{\frac{13}{6}}\left(a\sqrt{s}\right) + a\sqrt{s}K_{\frac{19}{6}}\left(a\sqrt{s}\right)\right)\right]. \qquad (4.60)
\end{aligned}$$

Here and below ${}_0F_1$ is the confluent hypergeometric limit function and ${}_1F_2$ is the generalized hypergeometric function, respectively [9]. Performing the expansions around $s = 0$, we find

$$\overline{W}(x,s) = \left(\frac{15}{4}\right)^{1/3} \frac{(3a^2+2ax+x^2)}{(a+x)^{2/3}} - 30^{1/3}\frac{3}{40}\frac{(54a^4+36a^3x+14a^2x^2-4ax^3-x^4)}{(a+x)^{2/3}}s + O(s^{7/6}), \tag{4.61}$$

$$\underline{W}(x,s)=\frac{9a^3+15a^2x+15ax^2+5x^3}{2\ 30^{2/3}(a+x)^{5/3}}+$$
$$\left(\frac{3}{100}\right)^{1/3}\frac{\left(81a^5+135a^4x+330a^3x^2+350a^2x^3+175ax^4+35x^5\right)}{140(a+x)^{5/3}}s+O\left(s^2\right), \tag{4.62}$$

and so

$$\lim_{s\to 0^+}\overline{W}(x,s)=\left(\frac{15}{4}\right)^{1/3}\frac{\left(3a^2+2ax+x^2\right)}{(a+x)^{2/3}},\quad \lim_{s\to 0^+}\underline{W}(x,s)=\frac{9a^3+15a^2x+15ax^2+5x^3}{2\ 30^{2/3}(a+x)^{5/3}}, \tag{4.63}$$

The latter yield

$$\frac{9a^3+15a^2x+15ax^2+5x^3}{20(a+x)}\le\hat{\tau}_4(x)\le\frac{3}{2}\left(3a^2+2ax+x^2\right). \tag{4.64}$$

5 Michaelis-Menten nonlinearity

The aim of this section is to obtain bounds for

$$\hat{\tau}_0(x)=\frac{1}{v(x)}\int_0^\infty (v(x)-u(t,x))\,dt \tag{5.1}$$

where u and v are solutions of the following problems

$$\begin{cases} u_t=u_{xx}-\frac{u}{1+u} & (t,x)\in(0,\infty)\times[0,\infty),\\ u_x(t,0)=-\alpha & t\in(0,\infty),\\ u(0,x)=0 & x\in[0,\infty), \end{cases} \tag{5.2}$$

and

$$\begin{cases} v_{xx}-\frac{v}{1+v}=0 & x\in[0,\infty),\\ v_x(0)=-\alpha, & v(\infty)=0, \end{cases} \tag{5.3}$$

respectively. Note that the solution of (5.3) is a bounded decreasing non-negative function, that is

$$0\le v(x)\le v_0<\infty, \tag{5.4}$$

which is given implicitly by

$$\int_v^{v_0}\frac{ds}{\sqrt{2(s-\ln(s+1))}}=x, \tag{5.5}$$

where the constant $v_0=v(0)$ solves

$$\sqrt{2(v_0-\ln(v_0+1))}=\alpha. \tag{5.6}$$

By direct application of the comparison principle to problem (5.2) we have

$$u(t,x)\ge 0\quad\text{on}\quad (t,x)\in[0,\infty)\times[0,\infty). \tag{5.7}$$

Next we set

$$w=v-u. \tag{5.8}$$

Subtracting equation (5.3) from (5.2) we have

$$\begin{cases} w_t=w_{xx}-\frac{w}{(1+v)(1+u)} & (t,x)\in(0,\infty)\times[0,\infty),\\ w_x(t,0)=0 & t\in(0,\infty),\\ w(0,x)=v & x\in[0,\infty). \end{cases} \tag{5.9}$$

Applying comparison principle to (5.9) we obtain $w\ge 0$ and thus

$$v\ge u. \tag{5.10}$$

Combining (5.4) and (5.10) we also have

$$0 \le u(t,x) \le v(x). \tag{5.11}$$

This observation allows to conclude that the functions $\overline{w}$ and $\underline{w}$ belonging to $\mathcal{A}$ and satisfying

$$\begin{cases} \overline{w}_t = \overline{w}_{xx} - \frac{\overline{w}}{(1+v)^2} & (t,x) \in (0,\infty) \times [0,\infty), \\ \overline{w}_x(t,0) = 0 & t \in (0,\infty), \\ \overline{w}(0,x) = v & x \in [0,\infty), \end{cases} \tag{5.12}$$

and

$$\begin{cases} \underline{w}_t = \underline{w}_{xx} - \frac{\underline{w}}{(1+v)} & (t,x) \in (0,\infty) \times [0,\infty), \\ \underline{w}_x(t,0) = 0 & t \in (0,\infty), \\ \underline{w}(0,x) = v & x \in [0,\infty), \end{cases} \tag{5.13}$$

are super and subsolutions for the problem (5.9), respectively.

One can verify by direct substitution into (5.12) that the function $v_0 e^{-(1+v_0)^{-2}t}$ is a supersolution. Therefore,

$$\underline{W}(x) = \int_0^\infty \underline{w}(t,x)dt, \quad W(x) = \int_0^\infty w(t,x)dt, \quad \overline{W}(x) = \int_0^\infty \overline{w}(t,x)dt, \tag{5.14}$$

are well-defined. Integrating (5.12) and (5.13) over t we then have

$$\begin{cases} \overline{W}_{xx} - \frac{\overline{W}}{(1+v)^2} = -v & x \in [0,\infty) \\ \overline{W}_x(0) = 0, \ \overline{W}(\infty) < \infty, \end{cases} \tag{5.15}$$

and

$$\begin{cases} \underline{W}_{xx} - \frac{\underline{W}}{(1+v)} = -v & x \in [0,\infty) \\ \underline{W}_x(0) = 0, \ \underline{W}(\infty) < \infty. \end{cases} \tag{5.16}$$

The accumulation time can be then estimated using solutions of (5.3), (5.15) and (5.16) as follows

$$\frac{\underline{W}(x)}{v(x)} \le \hat{\tau}_0(x) \le \frac{\overline{W}(x)}{v(x)}. \tag{5.17}$$

5.1 Heuristic arguments

As follows from linearization of (5.3) around $v = 0$, the solution of problem (5.3) will have the following behavior for $x \gg 1$:

$$v(x) = Re^{-x} + O(e^{-2x}) \tag{5.18}$$

for some constant $R > 0$. Next observe that for $x \gg 1$ equations (5.9), (5.15) and (5.16) reduce to

$$\begin{cases} W_{xx} - W = -Re^{-x} + \text{h.o.t.}, \\ W(\infty) < \infty, \end{cases} \tag{5.19}$$

This gives that for large x the solution reads:

$$W(x) = \left(\frac{Rx}{2} + C\right) e^{-x} + \text{h.o.t.}, \tag{5.20}$$

with some constant $C \in \mathbb{R}$.

Thus using (5.18) and (5.20) we have

$$\hat{\tau}_0(x) \approx \frac{W(x)}{v(x)} \approx \frac{x}{2} + K(x) \qquad x \gg 1, \tag{5.21}$$

where $K(x)$ is some function uniformly bounded on $[0,\infty)$.

5.2 Solution for problem (5.16)

We seek the solution of problem (5.16) in the following form:

$$\underline{W}(x) = v(x)\phi(x), \tag{5.22}$$

where $v(x)$ is the solution of (5.3). Substituting (5.22) into (5.16) after straightforward computations and taking into account (5.3) we have:

$$\begin{cases} \phi_{xx} + 2(\ln v)_x \phi_x = -1 \quad x \in [0, \infty) \\ \alpha\phi(0) = v(0)\phi_x(0), \end{cases} \tag{5.23}$$

and boundedness of $\underline{W}$ implies $\phi(x)$ grows no faster than $\big(v(x)\big)^{-1}$ as $x \to \infty$. From (5.23) follows (using v^2 as the integrating factor) that

$$\left(\phi_x v^2\right)_x = -v^2 \tag{5.24}$$

Integrating this equation from 0 to x and taking into account the boundary condition at $x = 0$ (see (5.23)), we have

$$\phi_x(x) = \frac{1}{v^2(x)}\left(\phi_x(0)v^2(0) - \int_0^x v^2(z)dz\right) \tag{5.25}$$

Taking a limit $x \to \infty$ of (5.25), using boundary condition in (5.23) at $x = \infty$ and taking into account that $v(x) \sim e^{-x}$ for large x we have

$$\phi_x(0) = \frac{1}{v^2(0)}\int_0^\infty v^2(z)dz \tag{5.26}$$

Integrating (5.25) from 0 to x and taking into account (5.26) and (5.23) we obtain

$$\phi(x) = \frac{\int_0^\infty v^2(z)dz}{\alpha v(0)} + \int_0^x \left(\int_y^\infty \left(\frac{v(z)}{v(y)}\right)^2 dz\right) dy \tag{5.27}$$

By the definition of the function ϕ in (5.22) we have

$$\phi(x) = \frac{\underline{W}(x)}{v(x)} \le \hat{\tau}_0(x) \tag{5.28}$$

and thus expression (5.27) serves as a lower bound for the accumulation time.

Now we use (5.27) to construct more explicit bound on $\hat{\tau}_0(x)$. To do so let us first show that the solution of (5.3) allows the following representation

$$v(x) = \rho(x)e^{-x}, \tag{5.29}$$

where ρ is some positive *increasing* function.

Substituting (5.29) into (5.3) we have

$$\rho_{xx} - 2\rho_x = -\frac{\rho^2 e^{-x}}{1 + \rho e^{-x}} \tag{5.30}$$

and thus

$$\left(\rho_x e^{-2x}\right)_x = -\frac{\rho^2 e^{-3x}}{1 + \rho e^{-x}} \tag{5.31}$$

Integrating this expression we have

$$\rho_x(x)e^{-x} = \left(\rho_x(0) - \int_0^x \frac{\rho^2(y)e^{-3y}}{1 + \rho(y)e^{-y}}dy\right) e^x. \tag{5.32}$$

Next, the boundary conditions in (5.3) give

$$\begin{aligned} &v_x(0) = -\alpha = \rho_x(0) - \rho(0), \\ &\rho_x(x)e^{-x} - \rho(x)e^{-x} = \rho_x(x)e^{-x} - v(x) \to 0 \quad \text{as} \quad x \to \infty. \end{aligned} \tag{5.33}$$

Since, $v(x) \to 0$ as $x \to \infty$ the second condition in (5.33) gives

$$\rho_x(x)e^{-x} \to 0 \quad \text{as} \quad x \to \infty. \tag{5.34}$$

Therefore, taking the limit $x \to \infty$ in (5.32) we obtain

$$\rho_x(0) = \int_0^\infty \frac{\rho^2(y)e^{-3y}}{1+\rho(y)e^{-y}}dy. \tag{5.35}$$

Substituting this result into (5.32) we have

$$\rho_x(x) = \int_x^\infty \frac{\rho^2(y)e^{2x-3y}}{1+\rho(y)e^{-y}}dy \geq 0, \tag{5.36}$$

so that

$$\rho_x(x) > 0 \quad x \in (0,\infty). \tag{5.37}$$

Next, observe that

$$\int_0^x \left(\int_y^\infty \left(\frac{v(z)}{v(y)}\right)^2 dz \right) dy = \int_0^x \left(\int_0^\infty \left(\frac{v(z+y)}{v(y)}\right)^2 dz \right) dy = \int_0^x \left(\int_0^\infty \left(\frac{\rho(z+y)}{\rho(y)}\right)^2 e^{-2z} dz \right) dy. \tag{5.38}$$

By (5.37) we have

$$\frac{\rho(z+y)}{\rho(y)} > 1 \quad \text{for all} \quad y > 0,\ z > 0. \tag{5.39}$$

It then follows immediately from (5.39) and (5.38) that

$$\int_0^x \left(\int_y^\infty \left(\frac{v(z)}{v(y)}\right)^2 dz \right) dy = \int_0^x \left(\int_0^\infty \left(\frac{\rho(z+y)}{\rho(y)}\right)^2 e^{-2z} dz \right) dy > \int_0^x \left(\int_0^\infty e^{-2z} dz \right) dy = \frac{x}{2} \tag{5.40}$$

Moreover, since ρ is an increasing function and using that $\rho(0) = v(0)$ we have

$$\int_0^\infty v^2(x)dx = \int_0^\infty \rho^2(x)e^{-2x}dx > \rho^2(0)\int_0^\infty e^{-2x}dx = \frac{v^2(0)}{2}. \tag{5.41}$$

Combining (5.40) and (5.41) we have from (5.27)

$$\phi(x) > \frac{v_0}{2\alpha} + \frac{x}{2}, \tag{5.42}$$

where $v_0 = v(0)$ and α are related by (5.6).

Finally, combining (5.42) and (5.28) we have

$$\frac{v_0}{2\alpha} + \frac{x}{2} < \hat{\tau}_0(x) \tag{5.43}$$

5.3 An upper bound for $\hat{\tau}_0(x)$

As a first step let us note that any function $W^\dagger$ satisfying the differential inequality

$$\begin{cases} W^\dagger_{xx} - \frac{W^\dagger}{(1+v)^2} + v \leq 0 & x \in [0,\infty) \\ W^\dagger_x(0) \leq 0,\ W^\dagger_x(\infty) < \infty, \end{cases} \tag{5.44}$$

is a supersolution for the problem (5.15) and thus

$$\overline{W}(x) \leq W^{\dagger}(x) \qquad x \in [0, \infty). \tag{5.45}$$

Consequently from (5.17) and (5.45) we have the following upper bound for the accumulation time

$$\hat{\tau}_0(x) \leq \frac{W^{\dagger}(x)}{v(x)} \tag{5.46}$$

Heuristic arguments (see sect. 5.1) strongly suggest that the accumulation time can be represented as $\frac{1}{2}x + C(x)$ where $C(x)$ is some uniformly bounded function. Guided by this intuition we look for the solution of the problem (5.44) in the following form:

$$W^{\dagger}(x) = \frac{1}{2}xv(x) + \frac{\psi(x)v(x)}{1+v(x)} \tag{5.47}$$

where $\psi(x)$ is a function to be determined. Substituting (5.47) into (5.44) and taking into account (5.3) and

$$\left(\frac{v}{1+v}\right)_x = \frac{v_x}{(1+v)^2}, \qquad \left(\frac{v}{1+v}\right)_{xx} = \frac{v}{(1+v)^3} - \frac{2v_x^2}{(1+v)^3}, \tag{5.48}$$

we obtain

$$\begin{cases} \psi_{xx} + 2\frac{v_x}{v(1+v)}\psi_x - \frac{2v_x^2}{v(1+v)^2}\psi + \frac{xv}{2(1+v)^2} + (1+v)\left(1+\frac{v_x}{v}\right) \leq 0, \quad x \in (0,\infty), \\ \frac{v_0}{2} - \frac{\alpha\psi(0)}{(1+v_0)^2} + \frac{v_0\psi_x(0)}{1+v_0} \leq 0, \;\; \psi_x(\infty) < \infty, \end{cases} \tag{5.49}$$

where v_x is given by the first integral of (5.3)

$$v_x = -\sqrt{2(v - \ln(1+v))}. \tag{5.50}$$

Now let us seek a solution for the inequality (5.49) in the form

$$\psi(x) = M - Pv(x) - Qxv(x), \tag{5.51}$$

where M, P and Q are constant to be determined. Substituting (5.51) into the first inequality of (5.49) and collecting terms containing v and xv as a common factor, we obtain that the first inequality in (5.49) holds, provided

$$Q = \frac{1}{2}\sup_{v\in(0,v_0]} \frac{v^2(1+v)}{v^2(1+v) + 2v_x^2}, \tag{5.52}$$

$$P = P_0 - P_1 M = \sup_{v\in(0,v_0]} \frac{2Q(2+v)v|v_x| + (v - |v_x|)(1+v)^2}{v^2(1+v)+2v_x^2} - 2\inf_{v\in(0,v_0]} \frac{v_x^2}{(1+v)(v^2(1+v)+2v_x^2)} M.$$

Substituting (5.51) into the second inequality of (5.49) we have

$$M \geq M_{bc} = \frac{v_0}{2\alpha}\left(\frac{(1+v_0)^2 + 2\alpha P_0(2+v_0) - 2Qv_0(1+v_0)}{1 + P_1 v_0(2+v_0)}\right) \tag{5.53}$$

Finally, we require positivity of the function ψ. Therefore

$$M \geq \sup_{x\in[0,\infty)} Pv(x) + Qxv(x) \tag{5.54}$$

Since

$$\sup_{x\in[0,\infty)} Pv(x) + Qxv(x) \leq P\sup_{x\in[0,\infty)} v(x) + Q\sup_{x\in[0,\infty)} xv(x) = Pv_0 + \frac{Q}{\sqrt{2}}\sup_{v\in[0,v_0]} v\int_v^{v_0} \frac{dz}{\sqrt{z - \ln(1+z)}}, \tag{5.55}$$

where we use representation of x as a function of v by integrating (5.50), we set

$$M \geq M_p = \frac{1}{1+P_1 v_0}\left(P_0 v_0 + \frac{Q}{\sqrt{2}}\sup_{v\in[0,v_0]} v\int_v^{v_0}\frac{dz}{\sqrt{z-\ln(1+z)}}\right). \tag{5.56}$$

Hence for $\psi(x)$ to be a non-negative solution of the problem (5.49) we can take

$$M = \max\{M_{bc}, M_p\}. \tag{5.57}$$

The above computations yield that an upper bound for the accumulation time reads

$$\hat{\tau}_0(x) \leq \frac{1}{2}x + \frac{M - Pv(x) - Qxv(x)}{1 + v(x)}, \tag{5.58}$$

with M given by (5.53), (5.56) and (5.57) and P, Q given by (5.52).

References

[1] L. C. Evans. *Partial Differential Equations*, volume 19 of *Graduate Studies in Mathematics*. American Mathematical Society, Providence, RI, 1998.

[2] J. Smoller. *Shock Waves and Reaction-Diffusion Equations*. Springer-Verlag, New York, 1983.

[3] M. E. Taylor. *Partial Differential Equations III: Nonlinear Equations*. Springer-Verlag, Berlin, 1996.

[4] M. H. Protter and H. F. Weinberger. *Maximum principles in differential equations*. Springer-Verlag, New York, 1984.

[5] W. Walter. Nonlinear parabolic differential equations and inequalities. *Disc. Cont. Dyn. Syst.*, 8:451—468, 2002.

[6] D. H. Sattinger. Monotone methods in nonlinear elliptic and parabolic boundary value problems. *Indiana Univ. Math. J.*, 21:979–1000, 1972.

[7] A. M. Berezhkovskii, C. Sample, and S. Y. Shvartsman. How long does it take to establish a morphogen gradient. *Biophys. J.*, 99:L59–L61, 2010.

[8] M. Abramowitz and I. Stegun, editors. *Handbook of mathematical functions*. National Bureau of Standards, 1964.

[9] G. Gasper and M. Rahman. *Basic hypergeometric series*. Cambridge University Press, 1990.